UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,270	05/18/2001	Esther H. Chang	2444-107	5176

6449 7590 08/14/2002

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER
CHEN, LIPING

ART UNIT	PAPER NUMBER
1632	8

DATE MAILED: 08/14/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,270	CHANG ET AL.	
	Examiner	Art Unit	
	Liping Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the claims

Claims 1-32 are pending and examined in this office action on the merits.

Priority

This is a 371 of PCT/US99/27365 (11/19/1998).
Provisional application 60/128,330 filed 04/08/1999.

DETAILED ACTION

Specification

The disclosure is objected to because of the following informalities:

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: Transferrin mediated viral delivery system for gene therapy.

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

The description of the drawings for Fig. 6 is objected to because there is no indication as what "TxT" stands for.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 13-18, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a vector comprising a transferrin non-covalently bound directly to the virus for delivery to a target cell that contains transferrin receptor and is out side of blood-brain barrier within a host animal, prepared by mixing virus with transferrin in a 10 mM HEPES buffer (specification, page 12, Example 1), does not reasonably provide enablement for a transferrin mediated vector for delivery of a transgene to any target cell or a transferrin containing cell that is protected by blood-brain barrier, nor enablement for preparing a vector by mixing any virus with any ligand in any aqueous medium for delivery to a target cell within a host animal including cells that are protected by blood-brain barrier. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is directed to a vector for delivery of a virus to a target cell within a host animal mediated by a targeting ligand that is non-covalently bound directly to the virus. However, the specification only provides evidence of mixing transferrin with adenovirus, retrovirus and Herpes simplex virus for vector preparation and delivery to target cells that are out side of blood-brain barrier (specification, page 12 –25, Example 1-10). There is no evidence or guidance as how

the transferrin bound vector can be used for delivery a transgene to a target cell that is protected by blood-brain barrier, nor evidence or guidance as any claimed ligands such as growth factors EGF, VEGF, FGF, IGF, or heregulin, hormones such as insulin, estrogen or progesterone, or any proteins such as toxins, or any specific viral protein that can be mixed with any virus in any aqueous medium or in the same medium where transferrin can be non-covalently bound to a virus to produce a vector that will deliver a transgene encoded by the virus to specific targeting cells including cells that are protected by blood-brain barrier encompassed by the claims.

Stryer et al. (Biochemistry, Fourth Edition, W.H. Freeman and Company, NY, 1995) teach that all biological structures and processed depend on the interplay of noncovalent interactions as well as covalent ones. The three fundamental noncovalent bonds are electrostatic bonds, hydrogen bonds, and van der Waals bonds (Stryer, page 7, first parag.). Stryer et al. also teach that water-soluble proteins fold into compact structures dependent on the primary structure of each protein (Stryer, page 33-35), such as myoglobin is folded mainly into α helices, whereas, ribonuclease A is folded mainly into β strands (Stryer, page 35, line 5-8). Stryer et al. further teach that [p]roteins as a class of macromolecules are unique in being able to recognize and interact with highly diverse molecules. Proteins are able in interact specifically with such a wide range of molecules because they are highly proficient at forming complementary surfaces and clefts. The rich repertoire of side chains on these surfaces and in these clefts enables proteins to form

hydrogen bonds, electrostatic bonds, and van der Waals bonds with other molecules (Stryer, page 39, third parag.). Some of the most interesting and important proteins contain multiple binding sites that communicate with each other. A conformational change induced by the binding of a molecule to one site in a protein can alter other sites more than 20 Å away. Thus, proteins can be built to serve as molecular switches to receive, integrate, and transmit signals (Stryer, page 40, first full parag.). Taken together, Stryer et al. teach that in a given solution, a protein's conformation is decided by its primary structure, and binding to a molecule, will cause a conformation change on a protein including sites that are involved in protein function such as receiving, integrating and transmitting signals. Although the specification demonstrates to produce vectors by mixing transferrin with several viruses, there is no evidence or guidance that under the same condition any other ligands claimed will bind to any virus. From the result that a transgene is specifically expressed in targeting cells when using a virus that has been incubated with transferrin (specification, page 12 –25, Example 1-10), one can conclude that transferrin is non-covalently bound to the virus during incubation and indeed direct the virus to targeting cells. However, the specification does not teach which binding force is involved in the noncovalent binding and what kind of conformation change occurred to transferrin after it binds to a virus. Since the target cells show a increased transgene expression when using transferrin bound vectors, (specification, Example 1-10), one can conclude that transferrin binding to a virus

does not induce a conformation change at the sites that are required for transferrin mediated endocytosis, taught by Stryer et al. (Stryer, page 39, third parag., page 40, first full parag , and page 938-939). However, there is no evidence or teaching that at the same buffer condition, all claimed ligands including all protein hormones such as growth hormones, and all non-protein hormones such as estrogen or progesterone will bind to a given virus non-covalently, and all bindings will be stable enough for delivery of the ligand-virus complexes into a host and the binding of a given ligand to a virus will not cause the ligand to have a conformation change at the sites that are required for the ligand to recognize and bind to its receptor. It is noticed that a higher transferrin/virion ratio is required for a vector preparation when the vector is used for *in vivo* transgene delivery such as mixing transferring with adenovirus at a ratio of 5000 TF/virion for *in vitro* transgene delivery, but 7.5 $X10^3$ to 1.5 X 10^5 Tf/virion (0.01-0.2 mg transferrin per 10^{10} virion, specification, page 15, line 23-24) for *in vivo* transgene delivery (specification, page 12-16, Example 1 and 2, and page 15 line 25-27). It is also noticed that a different transferrin/virion ratio is used when transferrin is mixed with a different virus for vector preparation, such as for retrovirus *in vivo* transgene delivery, a ratio of up to $1X10^6$ Tf/virion is used (specification, page 19, Example 6, especially page 20, line 4). Since for a same ligand and a same virus, different ligand/virion mixing ratio is required for preparing a vector for *in vitro* and *in vivo* transgene delivery, for a same ligand and a different virus *in vivo* transgene delivery, different ligand/virion

mixing ratio is also required, thus the skilled artisan will be required a undue amount of experimentation to first find a suitable buffer condition for the binding of a ligand to a given virus, and then find the best ligand/virion mixing ratio for *in vitro* transgene delivery and then increase the ratio to find a best mixing ratio for preparing vector for *in vivo* transgene delivery. To test if a virus-ligand complex is stable enough for *in vivo* transgene delivery, if a conformation change as a result of a ligand binding to a virus will alter its receptor recognition and binding function, the skilled artisan will be required to test each ligand mixing with each virus for *in vivo* transgene delivery and to observe the effect of the transgene expression using animal tumor models. Moreover, applicant claims to use different ligands for vector preparation and for cell-targeting (pertaining to claims 9, 11, and 12). However, there is no guidance as which type of tumors containing over expressed transferrin receptor or other claimed ligand receptors. Transferrin and all hormones are involved in physical function. Therefore, a ligand mediated cell targeting can only succeed when it is used for delivery a transgene to a tumor that is over expressing the ligand receptors. Further, with regard to gene therapy in brain, Castro et al. (Histol Histopathol. 16:1225-1238, 2001) teach that the brain offers a particular challenge for gene delivery to its constituent cells: it is encased by the skull, separated from the general circulation by the blood brain barrier, and made up of mostly non-dividing cells. The skull limits direct injection of vectors into the brain, the blood brain barrier inhibits the easy entry of vectors injected into the

bloodstream, and post mitotic target cells restrict what type of vector can be used to deliver genes to the brain (Castro, Abstract). Although the specification demonstrate transferrin mediated viral vector delivery to transferrin containing tumors, there is no evidence the transferrin mediated transgene delivery will benefit transgene delivery into blood-brain barrier. Thus, due to the lack of evidence and guidance for transferrin bound vector for transgene delivery to cells that are protected by blood-brain barrier, lack of evidence and guidance that other claimed ligands can also bind to a given virus non-covalently in the same buffer or a different buffer to form a virus-ligand complex, which is stable enough for transgene targeting cell delivery *in vivo*, and the conformation change resulted from the binding of the ligand to a virus, will not alter its receptor recognition and binding function, lack of guidance as which type of tumors are over expressing any claimed ligand receptors, the claimed invention would have required one skilled in the art to engage in an undue amount of experimentation without a predictable degree of success to achieve the invention as claimed.

Claims 19-32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In addition to the reasoning presented above in regarding to claims 1-11 and 13-18, these claims are not enabled because the specification only provides evidence of delivery an adenoviral vector encoding P53 to a target cell in an SCCHN Xenograft Nude mouse in conjunction with radiation treatment (specification, page 17-19, Example 4 and 5) or to a target cell in an immune competent B_{16} mouse of melanoma lung metastases model in conjunction with chemotherapy (specification, page 20, Example 7). There is no evidence or guidance as to delivery of a therapeutically effective amount of the same vector encoding P53 to cancer cells within a non-mouse patient, nor any vector encoding any transgene to other cancer cells such as bladder cancer, breast cancer, or brain cancer with or without in conjunction with radiation therapy or chemotherapy using encompassed by claims.

Cancer has been known for long time as a result of the accumulation of multiple abnormalities and a result of complex multistep process (Cooper, Oncogenes, Jones and Bartlett Publishers, 1990, page 4, last parag.) and many tumor oncogenes (Cooper, page 76, Table 5.1, page 89, Table 6.1 and page 112, table 8.1) and tumor suppressor genes (Cooper, page 132-135) have been recognized to be related with certain type of carcinomas. There is also evidence that environmental exposure related with cancer formation (Feigelson, et al. J. Cell. Biochem. 25S:15-22, 1996, Abstract). Corrective gene therapy is directed at preventing or reversing steps in the pathophysiology of the disease by insertion of a gene into disease tissue, which corrects a critical pathway in neoplasia (Carducci, page 225, third full parag.

line 1-6), and correcting one genetic defect in a multistep process of genetic hits may not be sufficient once the cancer has produced a fully invasive and metastatic clone (Carducci, page 226, third parag. line 6-8). Thus, besides the amount of vector to be delivered to a targeting cell, to reach a therapeutically effect, it needs to consider cancer type, cancer development steps and transgene used. However, the specification does not provide any guidance as to which type of cancer, at which step of cancer development, or which transgene should be used. Further, as indicated by the specification that a higher transferrin/virion ratio is required for a vector preparation when the vector is used for *in vivo* transgene delivery (specification, page 15, line 25-17) as observed from the result of *in vivo* delivery a transgene to mice, one can expect that to a bigger animal, the ratio that is used for transferrin/virion for mice delivery is still not enough according to the teaching of Hulme et al. (Receptor-Ligand Interactions, Oxford university press, 1992) as ligand-receptor binding is a continued process between association and dissociation which is influenced by ligand concentration (Hulme, page 65-67). Further, Orkin et al. (Report for The Third Meeting of The NIH Investment in Research on Gene Therapy, August, 1995) states that "Unfortunately, however, mouse models often do not faithfuloly mimic the relevant human conditions (Orkin, page 11, sec. full parag.). Orkin et al. Further states that "animal models are not satisfactory for studying many important human disorders, including cystic fibrosis, various cancers, and AIDS. Therefore, human studies are necessary ot develop effective

treatments for these and many other diseases" (Orkin, page 14, forth parag.). Due to multicauses and multisteps of a cancer development, lack of evidence and guidance as any transgene can be used for any type of cancer at any specific step of a cancer development, the mouse model used is not proven a faithfully mimic the relevant human conditions, lack of evidence that the same transferrin/virion ratio for vector preparation used for transgene delivery in mice can be applied to human, the claimed invention would have required one skilled in the art to engage in an undue amount of experimentation to achieving a therapeutic effective amount of a vector delivery to a targeting cell without a predictable degree of success to achieve the invention as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-4, 6-10, and 19-24 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Wickham et al. (U.S. Patent 5,962,311, filing date of 08/21/96, issued on 10/05/99).

Wichham ('311) teaches a recombinant virus such as adenovirus vector for gene transfer (col. 13, line 34-56) comprising a short-shafted fiber to increase the specificity of biding of the virus to a given cell by direct or indirect binding such as a bispecific or multispecific binding agent (col. 5, line 22-42), and a method of targeting the recombinant virus to a cell by contacting the virus vector with a bispecific or multispecific binding agent ('311, claim 60, and col. 22, line 25 to col. 24, line 27), such as an antibody that is selectively binds a binding domain of an adenoviral penton base or fiber knob and/or a cell surface binding site such as a cell surface receptor (col. 12, line 10-17 and line 30-31) by non-covalent interaction (col. 12, line 41-42). Thus Wichham clearly anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 5, 25, 27-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Wickham et al. (U.S. Patent 5,962,311, filing date of 08/21/96, issued on 10/05/99) in view of Zhang et al.(U.S. Patent 6,410,010 B1, issued on 06/25/2002).

Wichham ('311) teaches a recombinant virus such as adenovirus vector for gene transfer (col. 13, line 34-56) comprising a short-shafted fiber to increase the specificity of biding of the virus to a given cell by direct or indirect binding such as a bispecific or multispecific binding agent (col. 5, line 22-42), and a method of targeting the recombinant virus to a cell by contacting the virus vector with a bispecific or multispecific binding agent ('311, claim 60, and col. 22, line 25 to col. 24, line 27), such as an antibody that is selectively binds a binding domain of an adenoviral penton base or fiber knob and/or a cell surface binding site such as a cell surface receptor (col. 12, line 10-17 and line 30-31) by non-covalent interaction (col. 12, line 41-42). '311 does not teach using the vector to encode P53 tumor suppressor gene.

However, Zhang et al. ('010) teach using adenovirus encoding p53 for gene therapy for cancer cells with aberrant p53 functions ('010, col. 2, line 62 to col. 3, line 2) with or without receiving chemotherapy ('010, col. 9,line 33) or treated with radiation ('010, col. 22, line 3-5).

Thus, with the teaching of '311 and the teaching of '010, it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to use the vector of '311 to delivery p53 for gene therapy for the cancer cells with aberrant p53 functions given results of '010.

Conclusion

Claims 1-11 and 13-32 are not allowed.

Claim 12 is objected as depending on rejected claim 1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liping Chen, whose telephone number is (703) 305-4842. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time). Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Pauline Farrier, Patent Analyst, at (703) 305-3550. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

Liping Chen, Ph.D.
Patent Examiner
Group 1632

DEBORAH J. REYNOLDS
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600